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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,078	01/08/2004	David H. Reifsnyder	12441.00050/16331.004	6550

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EXAMINER	
ROOKE, AGNES BEATA	
ART UNIT	PAPER NUMBER
1656	
MAIL DATE	DELIVERY MODE
10/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/753,078	REIFSNYDER ET AL.	
	Examiner	Art Unit	
	AGNES B. ROOKE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *20-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/10/05, 2/16/06, 4/10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final office action is in response filed on 05/23/2008. The amendments to the claims are acknowledged.

Status of Claims

Claims 1-57 are pending. New claims 55-57 have been added. Claims 20-49 are withdrawn. Thus, claims 1-19 and 50-57 are pending and under examination.

IDS

IDS documents submitted on 01/10/05, 02/16/06, 04/10/08 have been reviewed and signed by examiner. Several references have been crossed out because they are missing the date of the publication or are cited under the wrong category.

Rejection Withdraw

The rejection of claims 1-19 and 50-54 under the 35 USC 112, second paragraph, is withdrawn in view of the amendments to the claims.

The rejection of claims 1-19 under 35 USC 112, second paragraph, is withdrawn in reference to the phrase “at least 200 grams” since the upper defining limit is not necessarily in the claims as presented.

New Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19, 50-54, and new claims 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 559 632.

EP 0 559 632 teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules. Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims.

EP 0 559 632 teaches that a TFPI preparation refolded and purified by the method disclosed therein was greater than 95% homogeneous suggesting that there was minimal misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts. There is also no evidence or indication that the preparation contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated.

The EP 0 559 632 publication teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules including Ala-TFPI (TFPI derivative) (p. 8, lines 44-52). Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims.

It would be obvious to one skilled in the art at the time the invention was made to prepare a composition that has at least 200 grams of TFPI because Diaz-Collier teaches the same preparation where the concentration of TFPI or its derivatives is 500

mg because the only difference in such preparations is the concentration of TFPI compound. One would be motivated to increase or decrease the concentration of TFPI or its derivatives depending on the need in regards to the preparation. But most importantly, still the limiting factor in such preparation is the concentration of less than 12% of TFPI that is modified.

Applicants responded that the instant invention teaches formulation of at least 200 grams of TFPI and that Diaz-Collier's preparation is only 500 miligrams, and that nowhere doses Diaz-Collier suggest that commercial quantities of at least 200 grams are produced. Further, Applicants agree that the feature "at least 200 grams" does not change the percentages of modified species allowed in the claimed preparations, however this feature does define the total quantity of TFPI in these preparations.

Examiner would like to point out that the method of making such preparation is not examined, but the composition itself is examined, and the composition of the instant invention and the composition of Diaz-Collier are the same expect that the concentrations differ. Examiner includes dependent claims in the instant rejection because the increase of the amount of the composition, here TFPI, would not change the characteristics of the invention or its function since still "less than about 12%" of the TFPI that is modified, is the limitation. Further, the measurements of modified species by different methods are not limiting factors by themselves that would point to distinguished patentability of the composition claimed, but those measurements are common methods and practices used by one skilled in the art.

Claim 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 559 632 view of U.S. 6,525,102.

EP 0 559 632 teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules including Ala-TFPI (p. 8, lines 44-52).

EP 0 559 632 teaches that a TFPI preparation refolded and purified by the method disclosed therein was greater than 95% homogeneous suggesting that there was minimal misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts. Further, there is also no evidence or indication that the preparation of the EP 0 559 632 contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, absent evidence to the contrary, it appears that the preparation of the '632 publication is patentably indistinguishable from that of the present claims.

EP 0 559 632 does not teach that the pharmaceutical compositions comprise 20mM sodium citrate, 300 mM L-arginine, and 5 mM methionine, pH 5.5.

However, the US 6,525,102 teaches a preparation comprising TFPI in sodium citrate buffer (Col. 3, lines 41-45) and that adding arginine to a TFPI preparation protects TFPI from aggregation (Col. 6, lines 8-55).

The U.S. 6,525,102 teaches that methionine can be added to TFPI preparations to protect the polypeptide against oxidation (Col. 10, lines 21-43).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the pharmaceutical composition comprising TFPI produced in the EP 0 559 632 to contain sodium citrate, L-arginine, and methionine as taught in the U.S. 6,525,102 patent. The EP 0 559 632 teaches a TFPI product that is patentably indistinguishable from that of the claims in its homogeneity. One of ordinary skill in the art would be motivated to add L-arginine and methionine to the pharmaceutical preparation of the EP 0 559 632 in order to preserve that homogeneity by preventing aggregation and oxidation during storage. The U.S. 6,525,102 patent teaches that it is well within the skill in the art to determine the concentration of these agents (Col. 8, lines 27-30). It was also well within the art to determine sodium citrate concentration that would buffer the acidity of L-arginine and lead to greater TFPI stability (a goal of the U.S. 6,525,102 patent). Thus, one would have been motivated to combine the teachings of the U.S. 6,525,102 patent and the EP 0 559 632 to optimize the TFPI stability after expression and purification.

Applicants responded that claim 19 is directed to a large scale composition comprising ala-TFPI, where less than 12% of the Ala-TFPI molecules are modified species, where the formulation comprises 20 MM sodium citrate, 300 mM L-arginine, and 5 mM methionine, at pH .5.5.Thus, Applicants state that Diaz-Collier neither describes nor suggests a large scale pharmaceutical formulation that has at least 200 grams of ala-TFPI, and that Chen fails to cure this deficiency.

Examiner responds that EP 0 559 632 teaches pharmaceutical compositions of 500 mg of TFPI protein that is purified by cation exchange chromatography. Even though Diaz-Collier does not teach concentration of TFPI or its derivatives to be at least 200 grams, it teaches 500 mg, where the limiting factor still remains that 12% of the TFPI or its derivatives that are modified species.

Further, the purpose of the Chen's reference was to point out that it is within the skill in the art to determine the agents that increase stability of TFPI as taught by Chen.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is 571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300. Information regarding the status of an application may be obtained from

the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

AR

/Karen Cochrane Carlson, Ph.D./

Primary Examiner, Art Unit 1656